

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68646 A1

(51) International Patent Classification⁷: C07D 417/12.
A61K 31/44, A61P 3/00

(74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline,
Corporate Intellectual Property, Two New Horizons Court,
Brentford, Middlesex TW8 9EP (GB).

(21) International Application Number: PCT/GB01/01131

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(22) International Filing Date: 14 March 2001 (14.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0006133.3 14 March 2000 (14.03.2000) GB

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*):
SMITHKLINE BEECHAM PLC [GB/GB]; New
Horizons Court, Brentford, Middlesex TW8 9EP (GB).

Published:

— with international search report

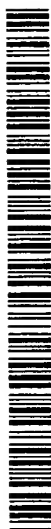
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): CRAIG, Andrew, Simon [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(54) Title: HYDROCHLORIDE SALTS OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

(57) Abstract: A substantially non-hydrated and non-hygroscopic or slightly hygroscopic hydrochloride salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione; a pharmaceutical composition containing such a compound, a process of preparing such a compound and the use of such a compound in medicine.



WO 01/68646 A1

HYDROCHLORIDE SALTS OF 5-[4-[2-(N-METHYL-N-(2-PYRIDYL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

5 European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter also referred to as "Compound I").

10 International Patent Application, Publication Number WO94/05659 discloses certain salts of the compounds of EP 0,306,228 and in particular the maleic acid salt.

It has now been discovered that Compound I forms a novel, non-solvated hydrochloride salt (hereinafter also referred to as the "Hydrochloride") that is particularly stable and hence is suitable for bulk preparation and handling. Surprisingly the
15 Hydrochloride is indicated to be non-hygroscopic and shows good aqueous solubility. Moreover, the Hydrochloride is stable in aqueous solution and does not dissociate therein. It can also be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

The novel Hydrochloride also has useful pharmaceutical properties and in
20 particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride characterised in that it:

- 25 (i) provides an infrared spectrum containing peaks at about 1745, 1516, 1257, 1056 and 803 cm^{-1} ;
(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at about 10.1, 13.4, 17.2, 22.2 and 29.4 $^{\circ}2\theta$; and/or
(iii) provides a Raman spectrum containing peaks at about 1314, 1242, 1185, 918 and
30 404 cm^{-1} .

In one favoured aspect, the Hydrochloride provides an infrared spectrum substantially in accordance with Figure I.

In one favoured aspect, the Hydrochloride provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure II.

35 In a further aspect, the Hydrochloride provides a raman spectrum substantially in accordance with Figure III.

The present invention encompasses the Hydrochloride isolated in pure form or when admixed with other materials.

Thus in one aspect there is provided the Hydrochloride in isolated form.

In a further aspect there is provided the Hydrochloride in pure form.

In yet a further aspect there is provided the Hydrochloride in crystalline form.

As indicated above the Hydrochloride is non-hygroscopic. The invention further
5 includes substantially non-hydrated and non-hygroscopic (or slightly hygroscopic)
hydrochloride salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
2,4-dione.

The invention also provides a process for preparing the Hydrochloride,
characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-
10 2,4-dione (Compound I) or a salt thereof, preferably dispersed or dissolved in a suitable
solvent, is reacted with a source of hydrogen chloride; and thereafter the Hydrochloride is
recovered.

Preferably, the reaction is carried out under anhydrous conditions, for example in
a dried nitrogen atmosphere.

15 A suitable solvent is an alkanol, for example propan-2-ol, or a hydrocarbon, such
as toluene, a ketone, such as acetone, an ester, such as ethyl acetate, an ether such as
tetrahydrofuran, a nitrile such as acetonitrile, or a halogenated hydrocarbon such as
dichloromethane.

Conveniently, the source of hydrogen chloride is a solution of hydrogen chloride
20 in an appropriate solvent, usually the reaction solvent, for example propan-2-ol.
Alternatively, the source of hydrogen chloride may be provided by concentrated
hydrochloric acid or aqueous dilutions of concentrated hydrochloric acid which are
suitably diluted so as to provide the required product, although concentrated hydrochloric
acid is preferred.

25 It is considered that the Hydrochloride can be produced in the above mentioned reactions
in the presence of small amounts of water but as stated the reaction is preferably carried
out under anhydrous conditions.

The reaction is usually carried out at ambient temperature or at an elevated
temperature, although any convenient temperature that provides the required product may
30 be employed. A preferred temperature is in the range of from 20-120°C, such as 30°C to
80°C, for example 70°C.

Recovery of the required compound generally comprises crystallisation from an
appropriate solvent, conveniently the reaction solvent, usually by cooling to a temperature
in the range of from 0°C to 40°C, for example 20°C.

35 In one preferred form the recovery comprises initial cooling to a first temperature,
such as 35°C to 70°C, preferably 50°C to 60°C, thereby allowing initiating crystallisation
and thereafter cooling to a second temperature, suitably in the range of 0°C to 40°C, to
complete crystallisation.

Crystallisation can also be initiated by seeding with crystals of the Hydrochloride but this is not essential.

Compound I is prepared according to known procedures, such as those disclosed in EP 0,306,228 and WO94/05659. The disclosures of EP 0,306,228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

When used herein the terms relating to hygroscopicity are used in accordance with known criteria as set out in J C Callahan et al., Drug Development and Industrial Pharmacy, 1982, 8(3), 355-69 which classifies hygroscopicity with respect to the % weight gain of a test compound under controlled conditions of temperature and humidity (25° C and 75% relative humidity) wherein the test compound has been allowed to attain an approximately constant weight: the following classification is used:

<u>% Weight Gain</u>	<u>Classification</u>
<2%	non-hygroscopic
2-10%	slightly hygroscopic
10-20%	moderately hygroscopic
>20%	very hygroscopic

For the avoidance of doubt when used herein the terms "non-hygroscopic", "slightly hygroscopic", "moderately hygroscopic" and "very hygroscopic" are to have the meanings defined by the above mentioned criteria.

Furthermore, the term "slightly hygroscopic" can particularly mean a compound showing a % weight gain under the above mentioned criteria of any one of 2-9%, 2-8%, 2-7%, 2-6%, 2-5%, 2-4% and 2-3%.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Hydrochloride for use as an active therapeutic substance.

5 More particularly, the present invention provides the Hydrochloride for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Hydrochloride may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Hydrochloride is generally as disclosed for Compound I in the above mentioned
10 publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Hydrochloride and a pharmaceutically acceptable carrier therefor.

The Hydrochloride is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by
15 the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral,
20 parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

25 Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar
30 agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending,
35 filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrochloride to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Hydrochloride for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

5 In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Hydrochloride may be taken in amounts so as to provide Compound I in suitable doses, such as those disclosed in EP 0,306,228 and WO94/05659.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

10 The following examples illustrate the invention but do not limit it in any way.

Example 1: Preparation of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride

- 5 A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (6.0 g) and propan-2-ol (120 ml) was stirred and heated to 50°C under a nitrogen atmosphere. A solution of hydrogen chloride in propan-2-ol (5-6 N, 5.0 ml) was added and the stirred mixture warmed to 70°C, at which point a clear solution was observed. After cooling to 45°C over a period of one hour the resulting cloudy solution was
- 10 warmed to 60°C and maintained at this temperature for a period of 1 hour. The resulting thick white suspension was cooled to 30°C and the solid product collected by filtration, washed with propan-2-ol (25 ml) and dried under vacuum, over phosphorus pentoxide for 16 hours to give the title compound as a white crystalline solid (5.7 g).

- 15 Melting point 168 –170°C

DSC: $T_{\text{onset}} = 166.6^{\circ}\text{C}$, $T_{\text{peak}} = 169.5^{\circ}\text{C}$

Elemental Analysis:

- | | | | |
|--|----------|---------|----------|
| 20 Found: | C; 54.88 | H; 5.16 | N; 10.56 |
| Theory: ($\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_3\text{SCl}$) | C; 54.89 | H; 5.12 | N; 10.67 |

Ionic chlorine: Determined as 9.0% wt/wt (theory for $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_3\text{SCl}$: 9.0% wt/wt).

- 25 Water content: Determined as 0.2% wt/wt using a Karl Fischer apparatus.

Example 2: Preparation of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione hydrochloride

- 30 A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4.0 g) and propan-2-ol (100 ml) was stirred and heated to 70°C. Concentrated hydrochloric acid (1.1 ml) was added to the stirred reaction mixture which was observed
- 35 to give a clear solution after approximately 3 minutes. The stirred solution was cooled to 58°C and then maintained at a temperature between 58 – 60 °C for 1 hour. The resulting white suspension was cooled to 30°C and the solid product collected by filtration, washed with propan-2-ol (20 ml) and dried under vacuum over phosphorus pentoxide for 64
- 40 hours to give the title compound as a white crystalline solid (4.3 g).

Hygroscopicity of the Hydrochloride

A sample of the hydrochloride salt (279 mg), prepared according to Example 1, was exposed to a 75 % relative humidity atmosphere at 21°C for a period of 43 days. The sample attained constant weight during this period. The percentage weight gain of the sample was observed to be 0.4 %.

Conclusion

The hydrochloride salt is non-hygroscopic.

10 Aqueous Stability and Solubility of the Hydrochloride

50mg of the salt was placed in a 20mL volumetric flask, and water added in 2.5mL aliquots. The sample was ultrasonicated at 21°C to aid dissolution after each subsequent addition of water and then examined. When a clear solution was obtained, the approximate solubility mg/mL was calculated. The solution was then examined at 15 hourly intervals for evidence of subsequent clouding or precipitation.

Water added total (mL)	Observation
2.5mL	Cloudy suspension
5.0mL	Predominantly clear, only partially cloudy
7.5mL	Clear solution obtained. Remained clear after standing at 21°C for a further 2 hours. Approx. solubility 7mg/mL

Conclusion

The white crystalline solid dissolved readily to give a clear solution with a good aqueous solubility. The solution subsequently remained clear with no evidence of precipitation or clouding of the solution. This data confirms a previous experiment on a different batch of the Hydrochloride that also evidenced good solubility and provided a clear solution with no evidence of precipitation or clouding of the solution

Characterising data recorded for the product of Example 1:**A Infrared**

The IR spectrum (Figure I) was recorded as a liquid paraffin mull using a Perkin-Elmer 1720x FTIR instrument at a resolution of 2 cm⁻¹. The spectrum obtained is shown in Figure I. Bands were observed at:

1745, 1696, 1641, 1609, 1544, 1516, 1331, 1313, 1289, 1257, 1243, 1230, 1203, 1185, 1157, 1073, 1056, 1032, 1015, 984, 918, 907, 873, 841, 811, 803, 772, 738, 714, 657, 618, 605, 560, 527 and 505 cm⁻¹.

B X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Hydrochloride (Figure II) was recorded using a using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator

current: 40 mA, Start angle: 2.0 °2 θ , End angle: 35.0 °2 θ , Step size: 0.02 °2 θ , Time per step: 10.0 seconds.

Characteristic XRPD angles and relative intensities are recorded in Table I.

5

Table I.

Diffraction Angle (°2 θ)	Relative Intensity (%)
10.1	4.9
11.8	15.2
12.4	8.1
13.4	24.7
14.0	4.5
14.6	2.6
15.0	10
16.1	38.2
16.3	91.6
17.2	28
17.7	69
18.1	49.5
19.3	14.2
19.6	46.1
20.4	14.2
20.9	6.9
21.2	24.9
22.2	100
22.4	72.5
22.7	36.4
23.6	98.2
23.8	79.8
24.8	49.1
25.5	10.6
26.1	18.9
26.4	35.9
27.1	35.2
27.4	22.9
28.1	32.6
29.4	32.9
30.0	18.8
30.6	21.4

31.1	11.8
32.1	20
32.6	20.5
33.0	19.8
33.9	23.5
34.5	29.6

C Raman

5 The Raman spectrum (Figure III) was recorded with the sample in a glass vial in a Perkin-Elmer 2000R FT-Raman system, at 4 cm⁻¹ resolution. Excitation was from a Nd:YAG laser (1064 nm) with a power output of 400mW. Bands were observed at: 3100, 3068, 2927, 2893, 2863, 1746, 1706, 1611, 1587, 1545, 1446, 1382, 1360, 1314, 1287, 1242, 1212, 1185, 1156, 1096, 1073, 1032, 1017, 984, 918, 828, 772, 741, 715, 659, 636, 619, 606, 527, 506, 471, 440, 404, 333, 302, 262 cm⁻¹.

10

15

20

25

30

35

Claims:

1. A substantially non-hydrated and non-hygroscopic or slightly hygroscopic hydrochloride salts of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione.
- 5 2. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride characterised in that it:
 - (i) provides an infrared spectrum containing peaks at about 1745, 1516, 1257, 1056 and 803 cm^{-1} ;
 - 10 (ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at about 10.1, 13.4, 17.2, 22.2 and 29.4 $^{\circ}2\theta$; and/or
 - (iii) provides a Raman spectrum containing peaks at about 1314, 1242, 1185, 918 and 404 cm^{-1} .
- 15 3. A compound according to claim 2, wherein the Hydrochloride provides an infrared spectrum substantially in accordance with Figure I.
4. A compound according to claim 2 or claim 3, wherein the Hydrochloride provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure II.
- 20 5. A compound according to any one of claims 2 to 4, wherein the Hydrochloride provides a raman spectrum substantially in accordance with Figure III.
6. A process for preparing the Hydrochloride according to claim 1, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a source of hydrogen chloride; and thereafter the Hydrochloride is recovered.
- 25 7. A process according to claim 6, wherein the reaction is carried out under anhydrous conditions.
- 30 8. A compound according to any one of claims 1 to 5, for use as an active therapeutic substance.
- 35 9. A compound according to any one of claims 1 to 5, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

10. A pharmaceutical composition comprising the Hydrochloride and a pharmaceutically acceptable carrier therefor.

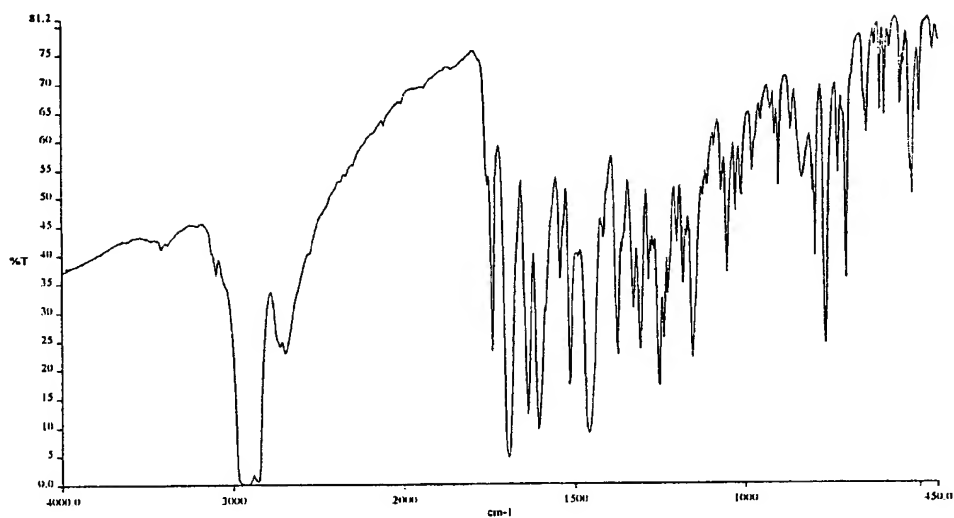
Figure 1 IR Spectrum (liquid paraffin mull) of the Hydrochloride

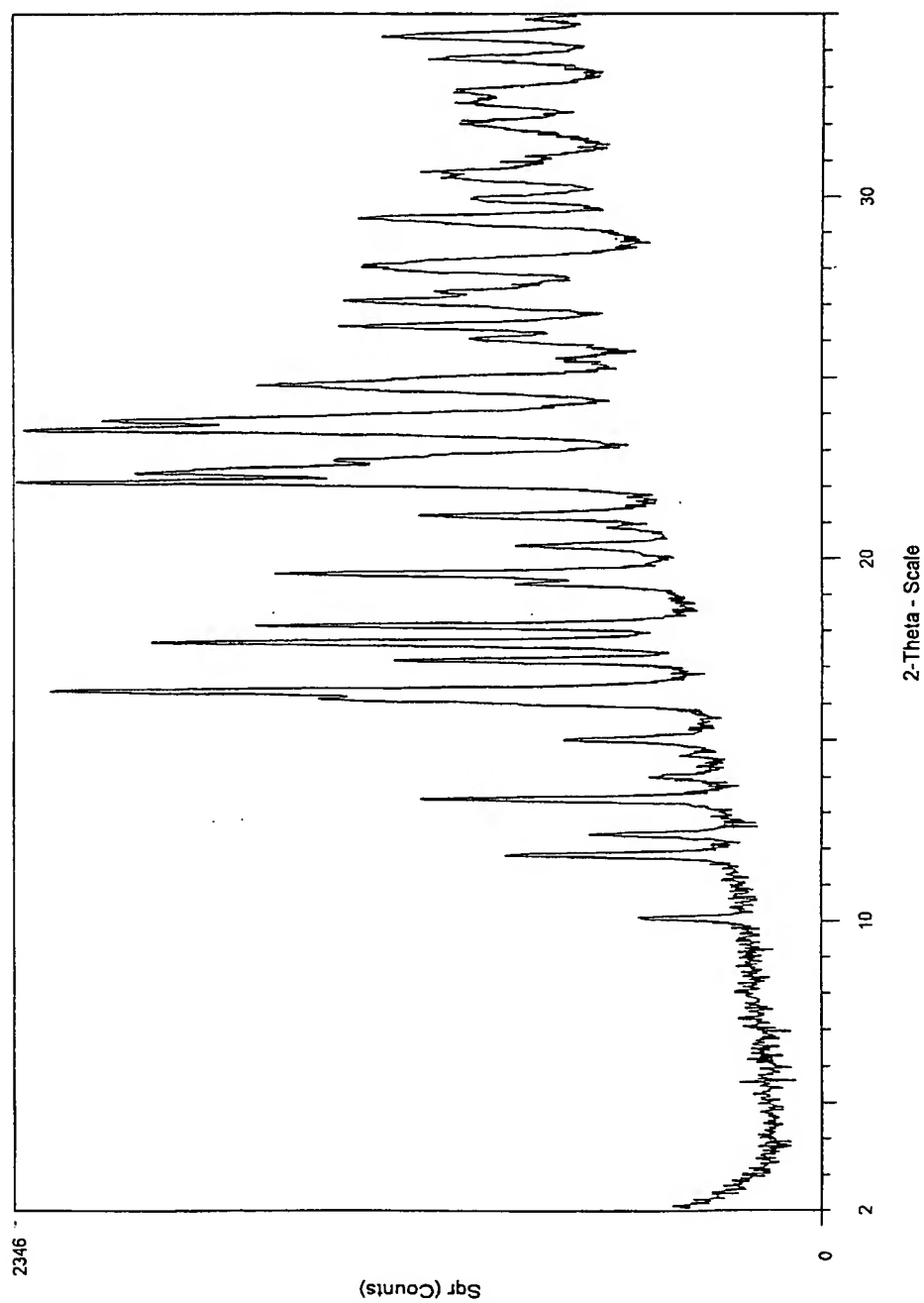
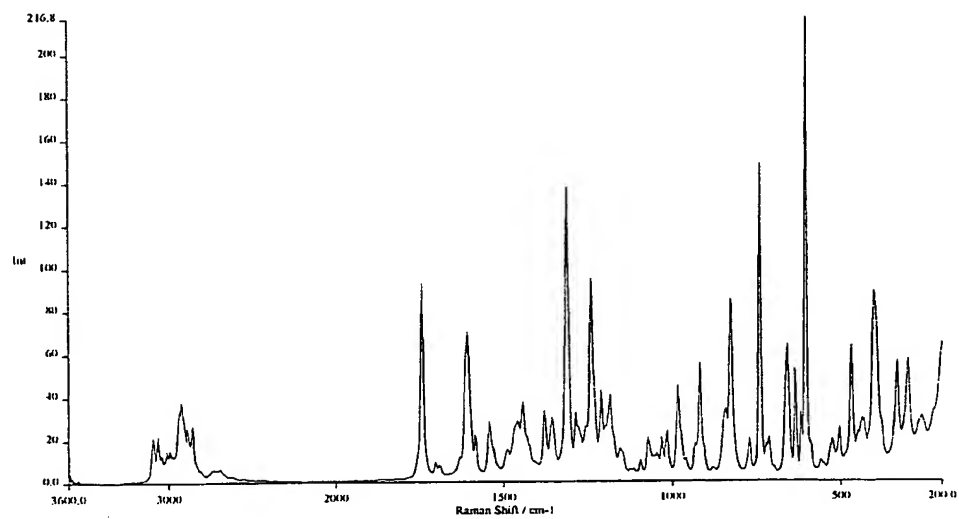
Figure II XRPD Pattern for the Hydrochloride

Figure III Raman Spectrum of the Hydrochloride

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01131

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/44 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) cited in the application page 1, line 20 - line 25 page 4, line 14 - line 16 ---	1-10
X	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application example 30 -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

5 June 2001

Date of mailing of the international search report

12/06/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fritz, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405659 A	17-03-1994	AP 513 A	30-07-1996
		AT 182147 T	15-07-1999
		AU 674880 B	16-01-1997
		AU 4973093 A	29-03-1994
		BR 1100916 A	04-07-2000
		CA 2143849 A	17-03-1994
		CN 1101911 A,B	26-04-1995
		CN 1183275 A,B	03-06-1998
		CN 1183413 A,B	03-06-1998
		CN 1183276 A	03-06-1998
		CZ 9500565 A	15-11-1995
		DE 69325658 D	19-08-1999
		DE 69325658 T	30-12-1999
		DK 658161 T	29-11-1999
		EP 0658161 A	21-06-1995
		EP 0960883 A	01-12-1999
		ES 2133410 T	16-09-1999
		FI 951004 A	03-03-1995
		FI 982413 A	06-11-1998
		GR 3030794 T	30-11-1999
		HK 1012363 A	05-05-2000
		HU 72639 A	28-05-1996
		IL 106904 A	30-09-1997
		JP 11147885 A	02-06-1999
		JP 2828777 B	25-11-1998
		JP 8501095 T	06-02-1996
		LU 90712 A	12-03-2001
		MX 9305397 A	31-01-1995
		NO 950852 A	03-03-1995
		NO 974646 A	03-03-1995
		NZ 255505 A	22-08-1997
		PL 307812 A	26-06-1995
		RU 2128179 C	27-03-1999
		SG 48302 A	17-04-1998
		SI 9300452 A	30-06-1994
		SK 27795 A	09-08-1995
		TW 385309 B	21-03-2000
		US 5741803 A	21-04-1998
		US 5910592 A	08-06-1999
		ZA 9306509 A	16-06-1994
EP 0306228 A	08-03-1989	AT 186724 T	15-12-1999
		AU 2173888 A	09-03-1989
		BR 1100841 A	20-06-2000
		CA 1328452 A	12-04-1994
		CA 1339902 A	09-06-1998
		CZ 9103916 A	17-03-1993
		DE 3856378 D	23-12-1999
		DE 3856378 T	11-05-2000
		DK 490288 A	05-03-1989
		DK 200001556 A	18-10-2000
		EP 0842925 A	20-05-1998
		ES 2137915 T	01-01-2000
		GR 3031873 T	29-02-2000
		JP 10194970 A	28-07-1998
		JP 10194971 A	28-07-1998
		JP 1131169 A	24-05-1989
		JP 2614497 B	28-05-1997

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0306228 A		JP 2817840 B	30-10-1998
		JP 9183771 A	15-07-1997
		JP 2837139 B	14-12-1998
		JP 9183726 A	15-07-1997
		JP 9183772 A	15-07-1997
		KR 164207 B	15-01-1999
		KR 164275 B	15-01-1999
		KR 169463 B	15-01-1999
		LU 90711 A	05-03-2001
		NZ 226027 A	26-03-1992
		PT 88410 A, B	31-07-1989
		SG 59988 A	22-02-1999
		US 5646169 A	08-07-1997
		US 5002953 A	26-03-1991
		US 5521201 A	28-05-1996
		US 5232925 A	03-08-1993
		US 5194443 A	16-03-1993
		US 5756525 A	26-05-1998
		US 5260445 A	09-11-1993
		ZA 8806536 A	26-07-1989